## REMARKS

Submission of this Amendment before examination of the application is requested.

Specification

During prosecution of the parent application, inconsistencies were noticed in two areas of the application as filed: page 30 of the specification and Figure 3.1. Amendments have been made to clarify these portions of the application, and the following remarks are presented in support of the amendments.

First, it was noticed that in the lower portion of Figure 3.1, the third codon from the end, "TGC" was shown as corresponding to "SER". This correspondence is not proper, as SER is properly coded for by TCG. A typographical error had apparently been made. Substitute Figure 3.1 corrects this inconsistency.

Second, in reviewing the description of plasmid pUT18 at page 30 of the specification, another inconsistency was noticed. The nucleotide sequence shown in paragraph 1 (SEQ ID No. 1) was incorrect because an "A" had been omitted from the 5′ end of the sequence. The entire sequence was properly shown in the Provisional Application No. 60/067,308, upon which this application relies for priority, and which is incorporated by reference.

It was also noticed that a "24-bp double-stranded oligonucleotide" is referred to, which includes SEQ ID No. 1 and its complementary sequence. However, SEQ ID No. 1 is actually only 23 bases in length (counting the omitted "A"). Thus, the "24" has been changed to --23-- in the specification.

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Applicants have also amended the application by inserting the attached Sequence Listing in place of the originally filed Sequence Listing. This change was made to include the changes to the sequence information discussed above. The originally filed Sequence Listing inadvertently did not include all of these changes.

This Preliminary Amendment, thus corrects these minor typographical errors and does not add any new matter.

Claims

The amendments to the claims change them only to conform to United States patent practice and also do not add new matter.

Drawings

The amendments to the drawings add the same identifiers defined in the Sequence Listing and which are added to the specification in this Preliminary Amendment. In addition, the amendment to the drawings of the sequence in Figure 3.1, merely corrects a typographical error in the sequence. The codon for the amino acid serine was incorrectly identified in the original drawing as "TGC." The correct codon is TCG," as indicated in the amended drawing.

If there is any fee due in connection with the filing of this Preliminary Amendment, please charge the fee to our Deposit Account No. 06-0916.

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Respectfully submitted,

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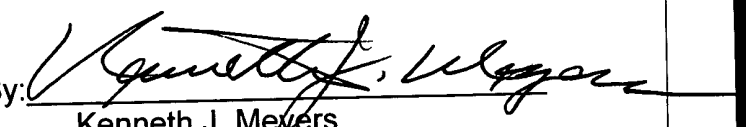
Dated: December 28, 2001

By: 

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**Appendix to the Preliminary Amendment of December 28, 2001**

Please amend the specification by replacing the first paragraph on page 30 with the following paragraph:

Plasmid pUT18 (3023-bp) is a derivative of the high copy number vector pUC19 (expressing an ampicillin resistance selectable marker and compatible with pT25 or pKT25) that encodes the T18 fragment (amino acids 225 to 399 of CyaA). In a first step, we constructed plasmid pUC19L by inserting a [24] 23-bp double-stranded oligonucleotide [(5'-ATTCATCGATATAACTAAGTAA-3' [SEQ ID No.:1])] (5'-AATTCATCGATATAACTAAGTAA-3' (SEQ ID No.: 1)) and its complementary sequence) between the *Eco*RI and *Nde*I sites of pUC19. Then, a 534-bp fragment harboring the T18 open reading frame was amplified by PCR (using appropriate primers and pT18 as target DNA) and cloned into pUC19L digested by *Eco*RI and *Cla*I (the appropriate restriction sites were included into the PCR primers). In the resulting plasmid, pUT18, the T18 open reading frame is fused in frame downstream of the multicloning site of pUC19. This plasmid is designed to create chimeric proteins in which a heterologous polypeptide is fused to the N-terminal end of T18 (see map).

Please amend the claims as follows:

6. (AMENDED) The signal amplification system [according to] as claimed in claim 4 [or 5], wherein the first and the second fragments are a fragment T25 corresponding to amino acids 1 to 224 of *Bordetella pertussis* CyaA and a fragment T18 corresponding to amino acids 225 to 399 of *Bordetella pertussis* CyaA.

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7. (AMENDED) The signal amplification system [according to any one of the claims] as claimed in claim 1 [to 3], wherein the modulating substance is a natural activator, or a fragment thereof, of the enzyme.

10. (AMENDED) A method of selecting a molecule of interest which is capable of binding to target ligand wherein the interaction between the said molecule of interest and the said target ligand is detected with a signal amplification system [according to any one of the claims] as claimed in claim 1 [to 9], by means of generating a signal amplification and triggering transcriptional activation.

13. (AMENDED) The method of selecting a molecule of interest [according to any one of claims] as claimed in claim 10 [to 12], wherein the signal amplification system comprises a bacterial multi-hybrid system of at least two distinct fragments of an enzyme, whose enzymatic activity is restored by the interaction between the said molecule of interest and the said target ligand.

14. (AMENDED) The method of selecting a molecule of interest [according to any one of claims] as claimed in claim 10 [to 12], wherein the signal amplification system comprises bacterial multi-hybrid system of at least a first fragment of an enzyme and a modulating substance, whose activity is restored by the interaction between the said molecule of interest and the said target ligand.

15. (AMENDED) The method of selecting a molecule of interest [according to any one of claims] as claimed in claim 10 [to 14], wherein the target ligand is selected from the group consisting of protein, peptide, polypeptide, receptor, ligand, antigen, antibody, DNA binding protein, glycoprotein, lipoprotein and recombinant protein.

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16. (AMENDED) The method of selecting a molecule of interest [according to any one of claims] as claimed in claim 10 [to 15], wherein the molecule of interest is capable of interacting with the target ligand and [possibly] optionally of binding to said target ligand.

17. (AMENDED) The method of selecting a molecule of interest [according to any one of claims] as claimed in claim 10 [to 16], wherein the interaction between the molecule of interest and the target ligand is detected, by means of signal amplification which triggers transcriptional activation, and is quantified by measuring the synthesis of the signaling molecule or the expression of the reporter gene.

21. (AMENDED) The method of selecting a molecule of interest [according to any one of claims] as claimed in claim 10 [to 20], wherein the molecule of interest is a mutant molecule compared to the known wild type molecule and said molecule of interest is tested for its capacity of interacting with the target ligand.

22. (AMENDED) The method of selecting a molecule of interest [according to any one of claims] as claimed in claim 10 [to 21], wherein the selection is performed in an *E. coli* strain, or in any bacterial strain deficient in endogenous adenylate cyclase or any other eukaryotic cell.

23. (AMENDED) A kit for selecting molecule of interest, wherein said kit comprises:

[(a)](A) a signal amplification system [according to any one of claims] as claimed in claim 1 [to 9];

[(b)](B) an *E. coli* strain, or in any bacterial strain deficient in endogenous adenylate cyclase or any other eukaryotic cell and;

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[(c)](C) a medium allowing the detection of the complementation selected from the group consisting of indicator or selective medium as minimal medium supplemented with lactose or maltose as unique carbon source, medium with antibiotics, medium to visualize fluorescence, conventional medium and medium which allows the sorting by the presence of the phage receptor.

24. (AMENDED) A kit for selecting a molecule of interest, wherein said kit comprises:

[(a)](A) a signal amplification system [according to any one of claims] as claimed in claim 1 [to 9] wherein the molecule of interest is a mutant molecule compared to the known wild type molecule and the known wild type molecule of interest is the control;

[(b) signal amplification system according to any one of claims 1 to 9 wherein the molecule of interest is the known wild type molecule as the control;]

[(c)](B) *E. coli* strain, or in any bacterial strain deficient in endogenous adenylate cyclase or any other eukaryotic cell and;

[(d)](C) a medium allowing the detection of the complementation selected from the group consisting of indicator or selective medium as minimal medium supplemented with lactose or maltose as unique carbon source, medium with antibiotics, medium to visualize fluorescence, conventional medium and medium which allows the sorting by the presence of the phage receptor for each signal amplification system;

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[(e)](D) means for detecting whether the signal amplification system with the mutant molecule is enhanced or inhibited with respect to the signal amplification system with wild type.

25. (AMENDED) A method of screening for a substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest wherein respectively the stimulating or the inhibiting activity is detected with a signal amplification system [according to any one of the claims] as claimed in claim 1 [to 9], by means of generating an amplification and respectively of triggering or of abolishing transcriptional activation, and wherein said signal amplification and said triggered or abolished transcriptional activation are compared with those obtained from an identical signal amplification system without any substance.

28. (AMENDED) The method of screening for a substance capable of stimulating the interaction between a target ligand and a molecule of interest [according to any one of claims] as claimed in claim 25 [to 27], wherein the signal amplification corresponds to the production of a signaling molecule.

29. (AMENDED) The method of screening for a substance capable of inhibiting the interaction between a target ligand and a molecule of interest [according to any one of claims] as claimed in claim 25 [to 27], wherein the signal amplification corresponding to the production of a signaling molecule is blocked or partially abolished.

30. (AMENDED) The method of screening for a substance capable of stimulating the interaction between a target ligand and a molecule of interest [according to any one of claims] as claimed in claim 25 [to 28], wherein the transcriptional activation leads to a reporter gene expression.

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31. (AMENDED) The method of screening for a substance capable of inhibiting the interaction between a target ligand and a molecule of interest [according to any one of claims] as claimed in claim 25 [to 27 and to claim 29], wherein the transcriptional activation leading to a reporter gene expression is blocked or partially abolished.

32. (AMENDED) The method of screening for a substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest [according to any one of claims] as claimed in claim 25 [to 31], wherein the target ligand is selected from the group consisting of receptor, ligand, antigen, antibody, DNA binding protein, glycoprotein and lipoprotein.

33. (AMENDED) The method of screening for a substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest [according to any one of claims] as claimed in claim 25 [to 32], wherein the substance is selected from the group consisting of protein, glycoprotein, lipoprotein, ligand and any other drug having stimulating or inhibitory affinity.

34. (AMENDED) The method of screening for a substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest [according to] as claimed in claim 28 [or 29], wherein the signaling molecule corresponds to the synthesis of cAMP.

35. (AMENDED) The method of screening for a substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest [according to] as claimed in claim 28 [or 29], wherein the signaling molecule corresponds to the synthesis of cGMP.

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36. (AMENDED) The method of screening for a substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest [according to] as claimed in claim 30 [or 31], wherein the reporter gene expression is selected from the group consisting of gene coding for nutritional marker such as lactose, maltose; gene conferring resistance to antibiotics such as ampicillin, kanamycin or tetracyclin; gene encoding for toxin; color marker such as fluorescent marker of the type of the Green Fluorescent Protein (GFP); gene encoding for phage receptor proteins or fragment thereof such as phage λ receptor, *lamB* and any other gene giving a selectable phenotype.

37. (AMENDED) The method of screening for a substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest [according to any one of claims] as claimed in claim 25 [to 36], wherein the molecule of interest is a mutant molecule compared to the known wild type molecule and said molecule of interest is tested for its capacity of interacting with the target ligand.

38. (AMENDED) The method of screening for a substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest [according to any one of claims] as claimed in claim 25 [to 37], wherein the screening is performed in an *E. coli* strain, or in any bacterial strain deficient in endogenous adenylate cyclase or any other eukaryotic cell.

39. (AMENDED) A kit for screening for a substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest, wherein said kit comprises:

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[(a)](A) a signal amplification system [according to any one of claims] as claimed in claim 1 [to 9] with the substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest, without any substance as the control;

[(b) a signal amplification system according to any one of claims 1 to 9 without any substance as the control;]

[(c)](B) *E. coli* strain, or in any bacterial strain deficient in endogenous adenylate cyclase or any other eukaryotic cell and;

[(d)](C) a medium allowing the detection of the complementation selected from the group consisting of indicator plate or selective medium as minimal medium supplemented with lactose or maltose as unique carbon source, medium with antibiotics, medium to visualize fluorescence, conventional medium, and medium which allows the sorting by the presence of the phage receptor and;

[(e)](D) means for detecting whether the signal amplification system with the substance is enhanced or inhibited with respect to the signal amplification system without any substance.

40. (AMENDED) A molecule of interest identified by the method of [any one of the claims] claim 10 [to 22].

41. (AMENDED) A molecule of interest corresponding to a polynucleotide capable of expressing a molecule which interacts with a fused target ligand coupled with an enzyme or a fragment thereof.

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42. (AMENDED) A substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest identified by the method [of any one of the claims] as claimed in claim 25 [to 38].

43. (AMENDED) The signal amplification system [according to any one of the claims] as claimed in claim 1 [to 9], wherein the bacterial multi-hybrid system contains:

[(a)](A) a first chimeric polypeptide corresponding to a first fragment a of an enzyme;

[(b)](B) a second chimeric polypeptide corresponding to a second fragment of an enzyme or a modulating substance capable of activating said enzyme and;

[(c)](C) a substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest, wherein the first fragment is fused to a molecule of interest and the second fragment or the modulating substance is fused to a target ligand and wherein the activity of the enzyme is restored by the interaction between the said molecule of interest and the said target ligand and wherein a signal amplification is generated.

44. (AMENDED) A polynucleotide [Polynucleotide] sequence coding for the signal amplification system [according to any one of the claims] as claimed in claim 1 [to 9], wherein the polynucleotide sequence codes for a bacterial multi-hybrid system of at least two chimeric polypeptides containing:

[(a)](A) a first chimeric polypeptide corresponding to a first fragment a of an enzyme fused to a molecule of interest;

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[(b)](B) a second chimeric polypeptide corresponding to a second fragment of an enzyme or a modulating substance capable of activating said enzyme fused to a target ligand.

45. (AMENDED) A polynucleotide [Polynucleotide] sequence coding for the signal amplification system [according to any one of the claims] as claimed in claim 1 [to 9 and to claim 43], wherein the polynucleotide sequence codes for a bacterial multi-hybrid system containing:

[(a)](A) a first chimeric polypeptide corresponding to a first fragment a of an enzyme fused to a molecule of interest;

[(b)](B) a second chimeric polypeptide corresponding to a second fragment of an enzyme or a modulating substance capable of activating said enzyme fused to a target ligand;

[(c)](C) a substance capable of stimulating or inhibiting the interaction between a target ligand and a molecule of interest.

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